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L3 ANSWER 1 OF 49

MEDLINE

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TITLE: **Rapamycin** specifically interferes with GM-CSF signaling in human **dendritic** cells, leading to apoptosis via increased p27KIP1 expression.

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AB The longevity of **dendritic** cells (DCs) is a critical regulatory factor influencing the outcome of immune responses. Recently, we demonstrated that the immunosuppressive drug **rapamycin** (Rapa) specifically induces apoptosis in DCs but not in other myeloid cell types.

The present study unraveled the mechanism used by Rapa to induce apoptosis

in human monocyte-derived DCs. Our data demonstrate that granulocyte-macrophage colony-stimulating factor (GM-CSF) preserves DC survival specifically via the phosphatidylinositol-3 lipid kinase/mammalian target of **rapamycin** (PI3K/mTOR) signaling pathway, which is abrogated by Rapa at the level of mTOR. Disruption of this GM-CSF signaling pathway induced loss of mitochondrial membrane potential, phosphatidyl-serine exposure, and nuclear changes. Apoptosis of

these nonproliferating DCs was preceded by an up-regulation of the cell cycle inhibitor p27(KIP1). Overexpression of p27(KIP1) in DCs using adenoviral gene transduction revealed that apoptosis is directly regulated

by p27(KIP1). Furthermore, both overexpression of p27(KIP1) and disruption

of the GM-CSF/PI3K/mTOR signaling pathway decreased the expression of the antiapoptotic protein mcl-1. This mTOR/p27(KIP1)/mcl-1 survival seems unique for DCs and may provide novel opportunities to influence immune responses by specific interference with the life span of these cells.

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DUPLICATE 1